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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,862	06/20/2003	Todd Zankel	30610/39383	8574

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,862	ZANKEL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-24* is/are pending in the application.

4a) Of the above claim(s) *10-13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *10-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Applicant's remarks and amendments filed 9 August 2005 have been entered. Claims 10 – 24 are pending.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

4. Claims 10 – 13, 15, and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 16 December 2004 and 18 March 2005.

Claims 14 and 17 – 24 are under examination in the instant office action.

Withdrawn Rejections and Objections

5. The following rejections or objections made in the previous office action are withdrawn:

The rejection of claims 14 and 17 – 24 under 35 USC 112 for not being enabled commensurate is scope with the claims. Applicant has amended the claims to require 80% identity to SEQ ID NO:1 and require that the conjugate protein bind LRP.

The rejection of claims 14 and 17 – 24 under 35 USC 112 for lacking written description. Applicant's amendments are sufficient to overcome the rejection.

The rejection of claim 21 under 35 USC 112 for containing new matter. Applicant indicated, both in the remarks filed 16 December 2004 and 9 August 2005, that support for PEGylation can be found on p. 33 of the specification. While the examiner did not find support on p. 33, there is support on p. 32, lines 5 – 10.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

6. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 20 recites the limitation of 5 to 30 amino acids. On p. 8 of the remarks filed 9 August 2005, applicant directs the examiner's attention to page 49, lines 7 – 22 as providing support for claim 20. However, the examiner is unable to find support for the specific range recited in claim 20 on those pages. Page 49, lines 7 – 9 provide support for linkers which are either 4 to 20 or 1 to 30 *atoms* long, whereas claim 20 as amended is drawn to about 5 to about 30 *amino acids*. Amino acids are molecules made up of a plurality of atoms; the ranges recited on p. 49 lines 7 – 9 clearly apply to atoms and not to amino acids. While amino acid linkers are contemplated on p. 49 lines 19 – 20, there is no contemplation of the range "about 5 to about 30 amino acids".

Claim Rejections - 35 USC § 103

7. Claims 14, 17, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell (1999. Clinical Genetics 55:389 – 394) in view of Czekay et al. (1997. Molecular Biology of the Cell 8:517-532, cited on the information disclosure statement filed 27 May 2004) for the reasons made of record on pp. 6 – 7 of the previous office action and reiterated herein.

Briefly, Russell teaches fusion proteins for treatment of diseases. Russell teaches that enzyme replacement is an important treatment for lysosomal storage diseases (p. 390, second column) and indicate that alpha glucosidase is a treatment of Pompe disease p. 390, Table 2). Russell et al. contemplate pharmaceutical compositions, as the entire paper is directed toward treatment of disease with recombinant proteins. Russell et al. do not teach agents comprising RAP. Czekay teaches RAP fusion proteins, and teaches that RAP is rapidly delivered to lysosomes. It would have been obvious to one of ordinary skill in the art to make a fusion protein between RAP and human alpha-glucosidase, with a reasonable expectation of success. The motivation would be to target the enzyme to the appropriate subcellular location, as suggested by Russell.

Applicant argues that one of ordinary skill in the art to combine the teachings of Russell with those of Czekay, and further argues that there would be no motivation to fuse GAA to RAP as GAA was already known to enter the lysosome. The examiner disagrees. First, Russell teaches that fusion proteins offer an advantage in that they permit intracellular targeting (p. 391, first sentence of first complete paragraph). Russell explicitly mentions lysosomal storage

diseases as being amenable to treatment by fusion proteins (see p. 393, where Russell states "The creation of proteins with novel functions, *via engineering and fusion*, will likewise broaden the applicability of recombinant proteins. *Lysosomal storage disorders are clear candidates for this therapeutic approach*" emphasis added). Russell mentions GAA as a treatment for Pompe disease (Table 2, p. 390) and teaches that there are difficulties in delivering proteins, such as enzymes to the intracellular region which can be overcome by the use of fusion proteins (see p. 390, bottom of second column). Clearly Russell provides the motivation to the artisan of ordinary skill to look elsewhere in the literature, as he teaches that GAA is a currently-known treatment for a lysosomal storage disease, and teaches that these diseases are particularly amenable to treatment with fusion proteins. Thus the artisan would be motivated to find proteins known to target the lysosome in order to more effectively treat Pompe disease.

Czekay teaches a protein which fulfills the role exactly. Czekay teaches that RAP is targeted to the lysosome, and that in order to enter the cell it binds to megalin, which is an endocytic receptor. Czekay also teaches the artisan of ordinary skill how to make fusion proteins comprising RAP (see p. 518, "Preparation of Fab Fragments of Anti-Megalin IgG and RAP-GST").

Applicant also argues that since GAA was known to enter the lysosome, as indicated by the abstracts from Van den Hout (2001), Winkel (2004), and Wan den Hout (2004) there would be no motivation to make the fusion protein. The examiner disagrees. Russell clearly pointed out that proteins do not enter cells well, even when encapsulated in liposomes, and that this problem could be overcome using fusion proteins. Applicant also argues that the creation of the fusion protein yields an unexpected result, namely the increased capacity of the fusion protein to enter the lysosome as compared to GAA alone. The examiner disagrees. Czekay clearly taught that RAP is targeted to the lysosome (see p. 520 "RAP but not Megalin is Delivered to Lysosomes"), and Russell provided the motivation to treat Pompe disease with a fusion protein.

Applicant also argues that the article by Warshawsky cited on p. 9 of the remarks teach away from the obviousness to combine the teachings of Russell and Czekay, since Warshawsky teaches that RAP is rapidly cleared from the plasma. The examiner disagrees. The paper by Warshawsky refers to a 39-kDa protein. RAP is an art-accepted synonym for this protein (see U.S. Patent 5,650,391, column 2 lines 1 – 17). Figure 4 from Warshawsky clearly indicates that RAP is indeed cleared rapidly from the blood; see also p. 940 first column where Warshawsky reports that 60% of RAP is cleared within 2 minutes of injection. This finding is not

inconsistent with the obviousness to use RAP to target GAA to cells. RAP is taken out of the bloodstream very quickly, and thus can rapidly find its way to the lysosomes in cells throughout the body. An artisan of ordinary skill would understand that this makes RAP an attractive target as a carrier of GAA, as the conjugate will easily pass out of the circulation and into the tissues where the enzyme can have its effect.

8. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Blattler et al. (1985. Biochem 24:1517-1524). Applicant did not traverse this rejection other than arguing non-obviousness to combine the teachings of Russell and Czekay. Thus the rejection is maintained for the reasons made of record in the previous office action.

9. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Davis et al. (U.S. Patent 6,072,041, issued 6 June 2000, filed 24 October 1997). Applicant did not traverse this rejection other than arguing non-obviousness to combine the teachings of Russell and Czekay. Thus the rejection is maintained for the reasons made of record in the previous office action. Note that Davis teaches linkers that are within the limitation of claim 20 as amended.

10. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Reddy (2000. Annals of Pharmacology 34:915-923). Applicant did not traverse this rejection other than arguing non-obviousness to combine the teachings of Russell and Czekay. Thus the rejection is maintained for the reasons made of record in the previous office action.

11. Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of either White et al. (U.S. Patent 5,962,266, issued 5 October 1999, filed 2 April 1997) or Strom et al. (U.S. Patent 6,165,476, issued 26 December 2000, filed 10 July 1997). Applicant did not traverse this rejection other than arguing non-obviousness to combine the teachings of Russell and Czekay. Thus the rejection is maintained for the reasons made of record in the previous office action.

Double Patenting

12. Claims 14, 17 – 20, and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 – 16 of copending Application No. 10/812,849, in view of Russell et al.

This rejection is maintained for the reasons made of record on p. 9 of the previous office action. Applicant argues that since 10/812,849 is a continuation-in-part of the present application it has a later effective filing date and thus could not have motivation to combine it with Russell to derive the claimed subject matter. The provisional double-patenting rejection was made because applicant has claimed the same subject matter in more than one application, independent of the filing date. Applicant stated he would address the double-patenting rejection at a later time (remarks, p. 11) and thus the rejection stands.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
September 13, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER